Remarks

The Examiner's withdrawal of the rejection of claims 1-7 under 35 U.S.C. §112 first paragraph-written description is appreciated. The Examiner's withdrawal of the rejection of claims 1-4 and 6-9 under 35 U.S.C. §102(b) is also appreciated.

Amendments to the Claims

Claim 1 has been amended to incorporate the limitation of claim 9. This amendment must be entered since claim 9 has been pending and examined on the merits. Rewriting claim 9 into independent form as claim 1 does not raise any new issues. Claim 10 has been similarly amended to incorporate the limitation of claim 16. Claims 9 and 16 have been cancelled. Claim 17 has been amended to depend from claim 10.

Rejection Under 35 U.S.C. § 112, first paragraph - enablement

Claims 1-5 and 9 were rejected under 35 U.S.C. § 112, first paragraph, as failing to meet the enablement requirement. Applicants respectfully traverse the rejection.

The Legal Standard

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under §112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See, e.g., Amgen v. Hoechst Marion Roussell*, 314 F.3d 1313 (Fed. Cir. 2003) and *Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d 1361, 1365, 42 USPQ2d1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). *See also In re Fisher*, 427 F.2d, 833, 839, 166 USPQ 18, 24

(CCPA 1970); *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); and *In re Stephens*, 529 F.2d 1343, 188 USPQ 659 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The adequacy of a specification's description is not necessarily defeated by the need for some experimentation to determine the properties of a claimed product. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F3d 956, 965-966, 63 USPQ2d 1609, 1614 (Fed. Cir. 2002). In addition, a patent need not teach, and preferably omits, what is well known in the art. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *citing Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984). Thus, information that is conventional or well-known to one of ordinary skill in the art need not be disclosed by the specification.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. *See In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re*

Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984). There is no requirement for examples. The Supreme Court also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling *In re* Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors " are illustrative, not mandatory. What is relevant depends on the facts."). As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. MPEP § 2164.01(b).

In *In re Douglas v. United States* 510 F.2d 364, 184 U.S.P.Q. 613 (Ct. Cl.1975) the Court of Claims noted that a patentee cannot "be expected to foresee every technological problem that may be encountered in adapting his idea to a particular use. Some experimentation and exercise of judgment is to be expected." Further, the Federal Circuit noted in *In re Wands*, "Enablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, citing *Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261, 270-71 (1916), wherein the court emphasized that some inventions cannot be practiced without adjustments being made to adapt them to the particular context. In such a situation, a specification is sufficient if it gives adequate guidance to one skilled in the art on how such adjustments are to be made.

Analysis

The claims define a drug formulation comprising a drug in an amount effective to provide relief from diseases and disorders of the breast in a pharmaceutically acceptable capable of delivering drug to the breast tissue; the carrier contains a penetration enhancer to promote delivery of the drug across the stratum corneum.

The specification at least from page 1, line 12, until page 2, line 16 describes disorders of the breast. The specification at least at page 7, lines 6-25 describes the drugs that can be incorporated into a formulation to treat diseases of the breast, and refers to the classification of pharmacologic agents and drugs in Goodman and Gilman, "The Pharmacological Basis of therapeutics", (9th Ed. McGraw-Hill Publishing Co.) (1996) ("Goodman and Gilman"). The drugs that fall within the classification of "chemotherapeutic agent", "hormones", "hormone releasing agent", "hormone analogue", "anti-estrogens", "LHRH analogues", and "anti-proliferative" agents are all known in the art (See for example, "Goodman and Gilman"). Furthermore, the specification from page 2, line 24 until page 4, line 27 provides examples of drugs that have been used to treat disorders of the breast. Thus, drugs that can be incorporated in the claimed formulation are not only disclosed in the specification, they are also well known in the art.

The examiner has provided no basis for his rejection other than an allegation that the claims are broad. This is not enough.

The specification discloses commonly used penetration enhancers that can be used to promote delivery of the drug across the stratum corneum at least at page 9, lines 1-16. Although

examples are not needed, the examples show enhanced permeation of danazol through the skin, in the presence of 5% oleyl alcohol.

The Examiner alleged that the state of the art with regard to a formulation comprising a drug with a penetration enhancer is underdeveloped, specifically stating that there does not appear to be any examples or teachings in the prior art in relation to a formulation similar to the claimed combination. An example in the prior art is not a requirement for enablement; indeed an example in the prior art would preclude patentability. The test for enablement is whether the specification teaches one of ordinary skill in the art how to make and use the claimed formulation without undue experimentation. The level of skill in the art with respect to drug formulations is high. The specification provides guidance as to what drugs and penetrations enhancers to select, in order to make the claimed formulation.

The Examiner further alleged that the state of the art indicates that there are problems with most known dermal penetration enhancers, citing International Publication No. WO 97/29735 by Reed, et al. ("Reed"), an application published over ten years ago. Applicants respectfully draw the Examiner's attention to the fact that dermal penetration enhancers which avoid the problems cited in Reed are also known in the art. In fact, one of the objects of the Reed application is to provide a safe skin-tolerant dermal penetration enhancer (see page 6, lines 10-11), and presumably this penetration enhancer has been known since Reed was published over ten years ago. Similarly, U. S. Patent Nos. 5,082,566, to Wong, et al., discloses penetration enhancers with less adverse/toxic effects. This was also published years before the filing date of this application. Reed also provides an exhaustive list of known penetration enhancers from

page 18, line 16 until page 19, line 15. Thus, although there are problems with some penetration enhancers, the prior art also provides penetration enhancers that avoid such problems. With the direction of what drugs and penetration enhancers to select provided in the specification, it is well within the abilities of one of skill in the art to select a drug and penetration enhancer as exemplified for danazol and 5% oleyl alcohol, in order to make the claimed formulation (see also, U.S. Patent No. 5,196,410 to Francoeur, et al., and U.S. Patent No. 4,861,764 to Samour, et al. or Reed).

Both the drugs and the penetration enhancers which are to be used in the claimed formulation are known to those skilled in the art and available. The specification provides additional evidence enabling one of skill in the art to make the claimed formulation. ***The examiner has also provided an abundance of additional evidence that suitable penetration enhancers are known to those skilled in the art.*** The only basis for the rejection is that the claims are broad. There is no evidence of any interaction between the drug and penetration enhancers. Mere breadth is insufficient legally to support a rejection under 35 U.S.C. 112. Therefore, claims 1-5 and 9 are enabled.

Rejection Under 35 U.S.C. §102

Claims 1, 2, 4-7 and 9 were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 4,919,937 to Mauvais-Jarvis, *et al.* ("Jarvis") as evidenced by U. S. Patent No. 5,580,857 to Oden ("Oden"). Applicants respectfully traverse this rejection.

Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc. v. Monoclonal Antibodies Inc.*, 231 USPQ 81 (Fed. Cir. 1986); *Scripps Clinic & Research Found. v. Genentech Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*:

Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. There must be *no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (18 USPQ2d at 1010, emphasis added).

Further, a reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation (see Id.).

Analysis

Jarvis

Jarvis discloses an anti-estrogen drug which is derived from tamoxifen, for treament of breast cancer. One can debate whether or not cancerous cells are breast tissue, but the claims have been amended to clearly exclude delivery of drugs for treatment of breast cancer, by incorporating the limitation of claim 9 and 16 into claims 1 and 10, wherein the disease is benign. As defined on MedicineNet.com, Definition of Benign:

Benign: Not cancer. Not malignant.

This difference alone excludes Jarvis. However, the Examiner alleged that Jarvis discloses 4-hydroxytamoxifen and triethanolamine, which is a penetration enhancer, citing Oden. Applicants agree with the Examiner that Oden discloses triethanolamine as an Example of a penetration enhancer. However, triethanolamine has many applications; for example, triethanolamine is commonly used in formulations as a ph adjuster/modifying agent (see for example U. S. Patent No. 6,730,323 to Murley et al. at col. 2, lines 20-35 and U.S. Patent No. 5,976,566 to Samour, et al., col. 6, line 46) and also, and as an emulsifier. Applicants are unclear as to the Examiner's reason for concluding that triethanolamine is employed as a penetration enhancer in Jarvis, considering the numerous other applications of the compound. There is nothing in Jarvis that supports such a conclusion. Furthermore, studies by Priborsky, et al., *Acta Univ. Palacki. Olomuc. Fac. Med.* 141:31-33 (1998) (a copy of which is attached) demonstrate that ethanolamine at concentrations similar to those employed by Jarvis *is not* effective as a penetration enhancer. Other studies by Gwak and Chun, *Int. J. Pharm.*, 236:57-64 (2002) ("Gwak") a copy of which is attached) show that triethanolamine at concentrations of 1% does not have penetration enhancing effects (Jarvis discloses a formulation containing about 1-1.5% triethanolamine). Thus, a disclosure of triethanolamine is not tantamount to the disclosure of a penetration enhancer. Jarvis is silent about the use of a penetration enhancer. A reference is considered as a whole, and there is nothing in Jarvis that would lead one of ordinary skill in that art to conclude that triethanolamine is used as a penetration enhancer or what concentration of triethanolamine would promote delivery of a drug across the stratum corneum; as discussed

above, the concentration of triethanolamine disclosed in Jarvis are not effective to enhance penetration (see Gwak). Therefore, claims 1, 2, 4-7, and 9 are novel over Jarvis.

Rejection Under 35 U.S.C. § 103

Claims 1-4 and 6-9 were rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 5,993,856 to Ragavan, et al. ("Ragavan 1"). Applicants respectfully traverse this rejection.

Legal Standard

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 U.S.P.Q. 459 (1966). The *Graham* analysis was recently affirmed on April 30, 2007 by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007). The Court recognized that a showing of "teaching, suggestion, or motivation " to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a).

The obviousness analysis requires looking at the invention as a whole. "Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986).

Hindsight analysis, such as picking and choosing from prior art references using the claimed invention as a template, has long been forbidden. *See e.g. In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988), stating "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." In *KSR*, the Court also warned against the use of hindsight analysis in making an obviousness determination. The Court stated, "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." (*KSR*, 127 S. Ct. at 1742, citing *Graham*, 383 U.S. at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "guard against slipping into the use of hindsight" (quoting M*onroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412, 141 U.S.P.Q. 549 (6th Cir. 1964)).

Analysis

The scope and contents of the prior art

Ragavan 1

Ragaven 1 discloses formulations for topical or local delivery for administration of drugs to a region such as the *reproductive organ* and the surrounding environs (Ragavan 1, col. 7, lines 37-40). Although Ragavan 1 discloses including standard excipients in the formulation (*See* col. 3, line 24-37), Ragavan 1 is silent about including penetration enhancers in the formulation. The formulations disclosed in Ragavan 1 comprise an effective amount of a drug for treating a region. "Region" is defined in Ragavan 1 as reproductive organs and their surrounding environs, which include uterus, fallopian tube, peritoneal space, pelvic cul-de-sac, ovaries, perineum and

the rectovaginal region (*See* Ragavan 1, at least at col. 7, lines 37-41). Thus, formulations disclosed in Ragavan 1 are meant for delivery across *mucosal membranes*, which does not present anywhere near the difficulty with respect to drug transport, into a region now known to be characterized by a unique vasculature, wherein the drug is relatively contained with a reproductive blood barrier so that effective levels can be achieved throughout the region, but without systemic levels being achieved. Transport across a mucosal surface into an isolated region is the not the same as, nor predictive of, transport through the skin and into the breast.

Differences between the prior art and the claims

Ragavan 1 does not recite all of the limitations of the claims.

Contrary to the formulation disclosed in Ragavan 1, the claimed formulations contain a drug in a pharmaceutically acceptable carrier capable of delivering the drug to the breast tissue in combination with a penetration enhancer, to promote delivery across the skin. Ragavan 1 does not disclose the claimed composition, as acknowledged by the Examiner in withdrawing the rejection of claims 1-4 and 6-9 under 35 U.S.C. §102(b) in view of Ragavan 1.

The Examiner alleged that Ragavan 1 discloses sorbitan esters and triethanolamine (which are penetration enhancers), which can be employed in the micro or nanoparticulate drug formulation disclosed in Ragavan 1. As discussed above, triethanolamine is an excipient which with numerous applications, depending on the concentration employed. Similarly, Oden at least at col. 7, lines 1-2 lists sorbitan monooleate derivatives as examples of emulsifying agents. Thus, mere listing of an excipient or chemical is not sufficient without intended use, since the intended use also influences the effective amounts of the compound needed, or without a clear

and unequivocable disclosure of a dosage which could have no other purpose. To illustrate this point, Alginic acid (at low concentrations of 5%) is widely used as a disintegrant promoting rapid breakdown of tablets to rapidly release the active agent (see the FMC BioPolymer Application bulletin retrieved from http://www.fmcbiopolymer.com/Portals/bio/Content/Docs/Pharmaceuticals/Alginic%20Acid%20102605.pdf. Retrieved 2/5/08, a copy of which is attached; See also, Oden, col. 6, lines 19-20). However, the same agent at higher concentrations is employed to delay release of active agent from formulations (See U.S. Published Application No. 20060141007 by Biesel et al.), the exact opposite effect obtained with a disintegrant.

Ragavan 1 is not concerned with delivery of drugs across the stratum corneum, and does not disclose penetration enhancers to promote delivery of any drug across the stratum corneum. A mere disclosure of triethanolamine or sorbitan esters as an excipient in Ragavan 1, is not tantamount to a disclosure of a penetration enhancer. A reference is considered as a whole. It is clear that the Examiner is focusing on the obviousness of substitutions and differences, instead of on the invention as a whole. The Supreme Court has made it clear that this is improper.

Nowhere in Ragavan 1 is there mention of a penetration enhancer. Common excipients used in drug formulations have more than a single application-thus the intended use of an excipient is relevant. Oden for example lists gelatin as a binding agent that can be used in solid dosage forms (see Oden, col. 6, line 15) and also lists gelatin as a suspending agent that can be used in liquid formulations (see Oden, col. 6, lines 24-27). The two formulations are different in spite of the fact that they utilize the same excipient. One of ordinary skill in the art will not

arrive at the conclusion that that triethanolamine or the sorbitan ester disclosed in Ragavan 1 is effective to enhance penetration across the stratum corneum. However, according to the Examiner, Ragavan 1 employs the same penetration enhancer as required by claim 1, and the same compound cannot have mutually exclusive properties. Applicants respectfully disagree with the Examiner. Ragavan 1 employs the same excipient, which may or may not function as a penetration enhancer. Triethanolamine/sorbitan esters are not invariably penetration enhancers. Triethanolamine can be a ph adjuster or an emulsifier or none of the above, depending on the concentrations employed.

For at least the reasons discussed above, Applicants submit that claims 1-4 and 6-9 are not obvious in view of Ragavan 1.

Double Patenting Rejection

Claims 1-9 were rejected under the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 and 31-33 of Ragavan 1, claims 1-4 and 17 of U.S Patent No. 6,652,874 to Ragavan, *et al.* ("Ragavan 2") and claims 1-3 and 12 of U.S. Patent No. 6,416,778 to Ragavan, *et al.* ("Ragavan 3"). Applicants respectfully traverse this rejection.

Legal Standard

When determining whether the claims of an application define an invention that is an obvious variation of an invention defined in the claims of a patent, the claims of the application are compared with the claims in the patent, the disclosure in specification of the patent is not considered in the analysis (*see* MPEP §§ 800-822). The MPEP explains that "[a] double patenting rejection of the obviousness-type is 'analogous to [a failure to meet] the

nonobviousness requirement of 35 U.S.C. § 103' except that the patent principally underlying the double patenting rejection is not considered prior art." MPEP § 804(II)(B)(1), citing *In re Braithwaite*, 379 F.2d 594, 154 U.S.P.Q. 29 (CCPA 1967). Therefore, analysis employed in an obviousness-type double patenting rejection parallels the guidelines for a 35 U.S.C. § 103 obviousness determination. *Id.*, citing *In re Braat*, 937 F.2d 589, 19 U.S.P.Q.2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985).

U.S. Patent No. 9,993,856 to Ragavan, et al. ("Ragavan 1")

Claims 1-9 were rejected under the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 and 31-33 of Ragavan 1. This rejection is improper based on a comparison of pending claims 1-9 with claims 1-15 and 31-33 of the Ragavan 1 as shown below.

Claims as Amended	Claims of Ragavan 1
1. A drug formulation comprising a drug in an amount effective to provide relief from benign diseases or disorders of the breast in a pharmaceutically acceptable carrier capable of delivering the drug to the breast tissue, comprising a penetration enhancer to promote delivery of the drug across the stratum corneum, wherein the drug is not a non-steroidal anti-inflammatory or analgesic. 2. The drug formulation of claim 1 wherein the drug is soluble in aqueous solutions.	1. A micro- or nano-particulate drug formulation for local or regional topical administration of an effective amount to provide relief from symptoms associated with a disease or disorder in a region in patients in need thereof, wherein the effective amount is less than the effective amount when the drug is administered systemically. 2. The formulation of claim 1 wherein the region is the female reproductive organs. 3. The formulation of claim 2 wherein the patients have a disorder located in the reproductive organs.

3. The drug formulation of claim 1 wherein the drug is in the form of micro- or nano-particulates. 4. The drug formulation of claim 1 wherein the carrier is selected from the group consisting of a gel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, and aerosol. 5. The drug formulation of claim 4, wherein the carrier is a hydroalcoholic gel. 6. The drug formulation of claim 1 wherein the drug is selected from the group consisting of chemotherapeutic agents, hormones, hormone releasing agents, hormone analogs, and anti-proliferative agents. 7. The drug formulation of claim 6 wherein the drug is selected from the group consisting of danazol, bromocriptine, tamoxifen, luteinizing hormone-releasing hormone (LHRH) analogues, and antiestrogens. 8. The drug formulation of claim 6 wherein the drug is a danazol.	4. The formulation of claim 1 wherein the formulation comprises drug particles. 5. The formulation of claim 3 wherein the drug is for treatment of endometriosis. 6. The formulation of claim 1 wherein the micro- or nano- particulates adhere to mucosal tissue. 7. The formulation of claim 1 where the micro- or nano- particulates comprise polymer altering rates of drug absorption in the region to be treated. 8. The formulation of claim 1 which can be administered vaginally, intraperitoneally, or directly on the reproductive organs of interest. 9. The formulation of claim 8 wherein the drug is danazol and wherein the formulation is suitable for vaginal administration in patients in need thereof and is in a dosage effective for treatment of endometriosis. 10. The formulation of claim 1 wherein the drug is an anticancer drug, cytotherapeutic or anti-proliferative drug in a dosage effective for treatment of cancer in the region of the patient where administered. 11. The formulation of claim 1 wherein the drug is an antiviral agent effective for treatment of viral infections selected from genital herpes and genital papilloma viral infections. 12. The formulation of claim 1 wherein the drug is

	an antifungal agent effective for treatment of vaginal fungal infections. 13. The formulation of claim 1 wherein the drug is an antibacterial agent effective for treatment of vaginal and endometrial bacterial infections. 14. The formulation of claim 1 wherein the drug is a steroid or steroid-like product suitable for treatment of endocrine conditions. 15. The formulation of claim 14 wherein the drug is effective for treatment of menopause, infertility, contraception, dysfunctional uterine bleeding, dysmenorrhea, adenomyosis, or assisted reproductive technologies. 31. A composition for treating endometriosis comprising danazole in a form promoting quick uptake into the blood stream when applied to the mucosal membranes of the female reproductive tract, wherein danazole is in a form delivering an effective amount to decrease the discomfort of endometriosis which is less than the effective amount when the drug is administered systemically. 32. The composition of claim 31 wherein the danazole is in a form selected from the group consisting of foams, tablets, and creams. 33. The composition of claim 32 wherein the danazole is in a form suitable for application to the

	uterus.

Independent claim 1 of Ragavan 1 defines a micro- or nano-particulate drug formulation for local or regional topical administration of an effective amount to provide relief from symptoms associated with a disease or disorder in a region in patients in need thereof, wherein the effective amount is less than the effective amount when the drug is administered systemically. Independent claim 31 of Ragavan 1 defines a composition for treating endometriosis comprising danazol in a form promoting quick uptake into the blood stream when applied to the mucosal membranes of the female reproductive tract, wherein danazol is in a form delivering an effective amount to decrease the discomfort of endometriosis which is less than the effective amount when the drug is administered systemically.

None of claims 1-15 and 31-33 of Ragavan 1 defines a formulation comprising a drug in a pharmaceutically acceptable carrier and penetration enhancer for delivery of an effective amount of the drug to the breast tissue.

None of the claims define a formulation comprising a drug and a penetration enhancer to promote delivery of the drug across the stratum corneum.

There is nothing in the claims of Ragavan 1 that leads one to make a formulation of a drug in combination with a penetration enhancer as claimed.

"Region" as recited in claim 1 of Ragavan 1 is defined as reproductive organs and their surrounding environs - which include uterus, fallopian tube, peritoneal space, pelvic cul-de-sac, ovaries, perineum and the rectovaginal region (*See* Ragavan 1, at least at col. 7, lines 37-41).

Thus, Ragavan 1 claims formulations for delivery across mucosal membranes. The Examiner has provided no reasons (*See* MPEP §804) why one of ordinary skill in the art would conclude that the claimed formulation (i.e. a formulation with excipients that promote delivery across the **skin**, a relatively non-permeable material), is an obvious variation of the formulations claimed in Ragavan 1 (i.e. formulations with excipients for delivery across mucosal membranes). Furthermore, there would be no motivation for one of ordinary skill in the art to modify the formulations claimed in Ragavan 1 to include a penetration enhancer as claimed.

In summary, the claims differ:

In drug to be delivered (for disorders of breast compared to urogenital and reproductive)

In region to be treated (reproductive, highly vascularized mucosal site, compartmentalized via a reproductive blood barrier in women vs. skin on breasts)

Need for excipient (no excipient vs. required to have penetration enhancer – which is determined by difference in properties of region, site of application)

For treatment of different disorders (preferably endometriosis vs. diseases of breast)

Therefore, claims 1-8 are non-obvious over claims 1-15 and 31-33 of Ragavan 1.

U.S Patent No. 6,652,874 to Ragavan, et al. ("Ragavan 2")

Claims 1-9 were rejected under the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 and 17 of Ragavan 2. This rejection is improper based on a comparison of pending claims 1-9 with claims 1-4 and 17 of the Ragavan 2 as shown below.

Claims as Amended	Claims of Ragavan 2
1. A drug formulation comprising a drug in an amount effective to provide relief from benign diseases or disorders of the breast in a pharmaceutically acceptable carrier capable of delivering the drug to the breast tissue, comprising a penetration enhancer to promote delivery of the drug across the stratum corneum, wherein the drug is not a non-steroidal anti-inflammatory or analgesic. 2. The drug formulation of claim 1 wherein the drug is soluble in aqueous solutions. 3. The drug formulation of claim 1 wherein the drug is in the form of micro- or nano-particulates. 4. The drug formulation of claim 1 wherein the carrier is selected from the group consisting of a gel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, and aerosol. 5. The drug formulation of claim 4, wherein the carrier is a hydroalcoholic gel. 6. The drug formulation of claim 1 wherein the drug is selected from the group consisting of chemotherapeutic agents, hormones, hormone releasing agents, hormone analogs, and anti-proliferative agents. 7. The drug formulation of claim 6 wherein the	1. A drug formulation, comprising drug particles suitable for local or regional administration of an effective amount of the drug to provide relief from symptoms in a region in patients in need thereof, wherein the effective amount is less than the effective amount when the drug is administered systemically and wherein the drug is selected from the group consisting of anticancer drugs, cytotherapeutic drugs, anti-proliferative drugs, and antiviral drugs. 2. The formulation of claim 1 wherein the region is the female reproductive organs. 3. The formulation of claim 2 wherein the patients have a disorder located in the reproductive organs. 4. The formulation of claim 1 wherein the drug is in the form of micro- or nano- particulates. 17. The formulation of claim 1, wherein the formulation is in a carrier promoting quick uptake of the drug into the blood stream, a carrier manipulating release of drug, or a carrier promoting adhesion of the drug, wherein the carrier is selected from the group consisting of a liquid suspension or dispersion, a hydrogel suspension or dispersion, a topical

drug is selected from the group consisting of danazol, bromocriptine, tamoxifen, luteinizing hormone-releasing hormone (LHRH) analogues, and antiestrogens. 8. The drug formulation of claim 6 wherein the drug is a danazol.	ointment, a cream, a lotion, and a foam.

Independent claim 1 of Ragavan 2 defines a drug formulation, comprising drug particles suitable for local or regional administration of an effective amount of the drug to provide relief from symptoms in a region in patients in need thereof, wherein the effective amount is less than the effective amount when the drug is administered systemically and wherein the drug is selected from the group consisting of anticancer drugs, cytotherapeutic drugs, anti-proliferative drugs, and antiviral drugs.

The same comments and analysis apply as above.

None of claims 1-4 and 17 of Ragavan 2 defines a formulation comprising a drug in a pharmaceutically acceptable capable of delivering the drug to the breast tissue.

None of the claims define a formulation comprising a drug and a penetration enhancer to promote delivery of the drug across the stratum corneum.

There is nothing in claims 1-4 and 17 of Ragavan 2 that leads one to make a formulation of a drug in combination with a penetration enhancer.

"Region" as recited in claim 1 of Ragavan 2 is defined as reproductive organs and their surrounding environs - which include uterus, fallopian tube, peritoneal space, pelvic cul-de-sac,

ovaries, perineum and the rectovaginal region (*See* Ragavan 2, col. 6, lines 32-39). Ragavan 2 claims formulations for delivery across mucosal membranes. The Examiner has provided no reasons (*See* MPEP §804) why one of ordinary skill in the art would conclude that the claimed formulation (i.e. a formulation with excipients that promote delivery across the skin), is an obvious variation of the formulations claimed in Ragavan 2 (i.e. formulations with excipients for delivery across mucosal membranes) when the requirements are so drastically different. Furthermore, there would be no motivation for one of ordinary skill in the art to modify the formulations claimed in Ragavan 2 to include a penetration enhancer as claimed.

Therefore, claims 1-8 are non-obvious over claims 1-4 and 17 of Ragavan 2.

U.S. Patent No. 6,416,778 to Ragavan, et al. ("Ragavan 3")

Claims 1-9 were rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 12 of Ragavan 3. This rejection is improper based on a comparison of pending claims 1-9 with claims 1-3 and 12 of the Ragavan 3 as shown below.

Claims as Amended	**Claims of Ragavan 3**
1. A drug formulation comprising a drug in an amount effective to provide relief from benign diseases or disorders of the breast in a pharmaceutically acceptable carrier capable of delivering the drug to the breast tissue, comprising a penetration enhancer to promote delivery of the drug across the stratum	1. A drug formulation comprising drug particles suitable for regional administration of an effective amount to provide relief from symptoms of a disease or disorder selected from the group consisting of endometriosis, endometrial bacterial infections, cancer, and endocrine conditions in a region in patients in

corneum, wherein the drug is not a non-steroidal anti-inflammatory or analgesic. 2. The drug formulation of claim 1 wherein the drug is soluble in aqueous solutions. 3. The drug formulation of claim 1 wherein the drug is in the form of micro- or nano-particulates. 4. The drug formulation of claim 1 wherein the carrier is selected from the group consisting of a gel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, and aerosol. 5. The drug formulation of claim 4, wherein the carrier is a hydroalcoholic gel. 6. The drug formulation of claim 1 wherein the drug is selected from the group consisting of chemotherapeutic agents, hormones, hormone releasing agents, hormone analogs, and anti-proliferative agents. 7. The drug formulation of claim 6 wherein the drug is selected from the group consisting of danazol, bromocriptine, tamoxifen, luteinizing hormone-releasing hormone (LHRH) analogues, and antiestrogens. 8. The drug formulation of claim 6 wherein the drug is a danazol.	need thereof, wherein the region is selected from the group consisting of the uterus, fallopian tubes, peritoneal space, pelvic cul-de-sac, ovaries, and urinogenital tract, wherein the effective amount is a dosage which results in low serum drug levels and reduced side effects as compared to systemic administration of the drug, and wherein the formulation is in a carrier promoting quick uptake of the drug into the blood stream, a carrier manipulating release of drug, or a carrier promoting adhesion of the drug selected from the group consisting of a liquid suspension or dispersion, a hydrogel suspension or dispersion, a topical ointment, a cream, a lotion, and a foam. 2. The formulation of claim 1 wherein the region is the female reproductive organs. 3. The formulation of claim 2 wherein the patients have a disorder located in the reproductive organs. 12. A composition for treating endometriosis comprising particulate danazole in a carrier promoting quick uptake of the drug into the blood stream, a carrier manipulating release of drug, or a carrier promoting adhesion of the drug, when applied to the mucosal membranes

	of the female reproductive tract, wherein the carrier is selected from the group consisting of a liquid suspension or dispersion, a hydrogel suspension or dispersion, a topical ointment, a cream, a lotion, and a foam wherein the dosage of the danazole is effective to reduce the symptoms of endometriosis without causing blood levels of danazole achieved with systemic administration of the danazole.

Independent claim 1 of Ragavan 3 defines a drug formulation comprising drug particles suitable for regional administration of an effective amount to provide relief from symptoms of a disease or disorder selected from the group consisting of endometriosis, endometrial bacterial infections, cancer, and endocrine conditions in a region in patients in need thereof,

wherein the region is selected from the group consisting of the uterus, fallopian tubes, peritoneal space, pelvic cul-de-sac, ovaries, and urinogenital tract, wherein the effective amount is a dosage which results in low serum drug levels and reduced side effects as compared to systemic administration of the drug, and

wherein the formulation is in a carrier promoting quick uptake of the drug into the blood stream, a carrier manipulating release of drug, or a carrier promoting adhesion of the drug selected from the group consisting of a liquid suspension or dispersion, a hydrogel suspension or dispersion, a topical ointment, a cream, a lotion, and a foam.

Independent claim 12 defines a composition for treating endometriosis comprising danzole and a carrier. Danazole was not known to be useful for the treatment of benign disorders or diseases of the breast at the time this application was filed.

None of claims 1-3 and 12 of Ragavan 3 defines a formulation comprising a drug in a pharmaceutically acceptable carrier capable of delivering the drug to the breast tissue.

None of the claims define a formulation comprising a drug and a penetration enhancer to promote delivery of the drug across the stratum corneum.

There is nothing in the claims of Ragavan 3 that leads one to make a formulation of a drug in combination with a penetration enhancer which enhances transport through the skin since the patent teaches administration to the mucosa.

"Region" as recited in claim 1 of Ragavan 3 is defined as reproductive organs and their surrounding environs - which include uterus, fallopian tube, peritoneal space, pelvic cul-de-sac, ovaries, perineum and the rectovaginal region (*See* Ragavan 3, col. 6, lines 28-34). Thus, Ragavan 3 claims formulations for delivery across mucosal membranes. The Examiner has provided no reasons (*See* MPEP §804) why one of ordinary skill in the art would conclude that the claimed formulation (i.e. a formulation with excipients that promote delivery across the skin), is an obvious variation of the formulations claimed in Ragavan 3 (i.e. formulations with excipients for delivery across mucosal membranes). Furthermore, there would be no motivation for one of ordinary skill in the art to modify the formulations claimed in Ragavan 3 to include a penetration enhancer as claimed.

Therefore, claims 1-9 are non-obvious in view of claims 1-3 and 12 of Ragavan 3.

Withdrawal of the nonstatutory double patenting rejection of claims 1-9 is respectfully solicited.

Rejoinder of all claims and allowance of claims 1-8, 10-15, and 17-19, as amended, is respectfully solicited.

Respectfully submitted,

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